Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

October 2-4, 2002

Session I

1. Topic and Author

"Clinical Diagnosis of Angina – The WISE Experience."
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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

a. Women referred for coronary angiography have a lower likelihood of coronary artery disease than men. Chest pain is one of the most frequent complaints encountered by the emergency physician. Each year, over 5 million patients appear in US emergency rooms with chest pain symptoms. Among the patients that receive coronary angiograms, about 85% of men and anywhere from 33% to 50% of women are actually found to have severe coronary artery obstructions (1-2). This fact was first documented in the 1980's in the Coronary Artery Surgery Study (CASS) and is partly due to lower prevalence of CAD among women (3). In the WISE study, 39% of the women have CAD, defined as $\geq$50% stenosis in $\geq$1 coronary artery almost all of whom (97%) had symptoms suggestive of myocardial ischemia.

b. Women have different symptom presentations than men. Early reports from the CASS study suggested that the chest pain constellation of *typical angina* (substernal pain, precipitated by emotional stress or physical exertion, relieved within 10 minutes by rest or nitroglycerin), was predictive of coronary artery disease (CAD) in both men and women (4-5). However, subsequent experience has questioned the suggestion that men and women have similar symptom patterns of CAD. Studies have shown that women with chronic stable angina are more likely than men to experience angina during rest, sleep, or mental stress. Women with CAD often experience symptoms in locations other than the substernum: lower jaw and teeth, both arms, shoulders, back, and epigastrum. Symptoms may include dyspnea, palpitations, presyncope, fatigue, sweating, nausea, or vomiting. For women, as opposed to men, having "typical angina" does not mean that they have CAD; conversely, many women with CAD do not have "typical angina" but experience a variety of "nonanginal" symptoms (6-10).

c. Typical Angina – WISE Findings. The Women's Ischemia Syndrome Evaluation (WISE) study is an NHLBI-sponsored 4-center study designed to optimize symptom evaluation and diagnostic testing for coronary artery disease (CAD) in women and explore mechanisms for symptoms in the absence of CAD (11). A total of 938 women undergoing coronary angiography were consecutively enrolled between 1996 and 2000. Baseline evaluation included quantitative angiographic evaluation, demographic characteristics, medical examination and history, reproductive history and status, CAD risk factors, psychosocial and functional capacity assessment, blood lipid and reproductive hormone levels, as well as a number of traditional and innovative evaluations for microvascular ischemia.

We evaluated symptoms in 557 WISE participants who had no prior history of myocardial infarction or revascularization and who had experienced chest or other discomfort suggestive of ischemia during the prior year. Ages ranged from 21 to 85 years (mean 57 $\pm$ 11) years, 73% were postmenopausal, and 17% were non-white (primarily African American). Although only 26% of this population had angiographically significant

CAD (≥50% stenosis in ≥ 1 coronary artery), there was a high rate of CAD risk factors (Table 1).

Symptoms were classified according to the three criteria developed by Diamond (12): is the discomfort substernal; is it precipitated by emotional stress or exertion; is it relieved by rest or nitroglycerin? *Typical angina* was defined as a "yes" response on all three questions; *atypical angina* a "yes" response on two of the questions; symptoms were defined as *nonanginal* with only one "yes" response. We also classified women with symptoms which could not be defined by any of the three criteria as *asymptomatic* of angina. This latter group of women was by no means symptom free but described a large variety of other types of discomfort.

Table 2 shows the relationship between anginal symptoms and CAD in this population of WISE women. There are several items of note.

(i) Although only 26% of the women had angiographically determined significant CAD, 70% had either typical or atypical angina.

(ii) Consistent with prior findings (15), women with CAD had a decreasing rate of typical angina (43%), atypical angina (31%), non-anginal symptoms (24%), and asymptomatic angina (2%). Moreover, women with CAD had higher rates of typical angina than those without CAD (p=0.003), and those without CAD were more likely to be asymptomatic (p=0.006).

(iii) Atypical angina rates did not differ in women with and without CAD. In fact, when combining typical and atypical angina, women with and without CAD were almost identical.

(iv) Although women with CAD had a higher rate of typical angina, 30% of the women without CAD also had typical angina. Typical angina had a sensitivity of 43% and therefore missed more than half of the women with angiographic diagnosis of CAD.

We determined predictive accuracy by stratifying CAD prevalence across age groups and anginal classifications using the same age categories used by Diamond (4). Among women aged 35-45 and 45-55 years, typical, atypical, and nonanginal symptoms resulted in an equal distribution of CAD prevalence, while the so-called asymptomatic women had indeed less CAD. Typical angina was no better than chance in predicting CAD among these younger women. Beyond age 55, the angina classification became more accurate with each increasing decade of age. A break-down of typical angina and its components by younger (< age 55) and older (≥55) women illustrates this discrepancy between the two age groups (table 3). Among younger women, substernal pain, effort/stress trigger, relief by rest or nitroglycerin, as well as typical angina did not differ among those with and without CAD. By contrast, older women with CAD had a significantly higher rate of these symptoms. The reason for this age difference are not clear. There is some speculation that as women age and lose the heart protection of their endogenous reproductive hormones, the pathophysiology of ischemic heart disease may become more similar to that of men. Furthermore, the symptoms experienced by women without CAD may in fact be signs and symptoms of microvascular ischemia. A more skeptical assessment suggests that these results can be explained by selection, or verification, bias.

d. Verification Bias in WISE. Before undergoing coronary angiography, a patient generally passes through a number of filters as he or she progresses from primary care, to various non-invasive screening tests, to the cardiologist. At each stage, someone must decide, based on the results of these evaluations, whether this patient should be referred to the cath lab. As a result, diagnosis or verification of disease status is only available for a sub-sample of symptomatic patients. This sub-sample is likely to have a higher rate of positive symptoms and abnormal non-invasive test results and to have a higher prevalence of disease (CAD) as compared to the population of patients evaluated for symptoms but lacking verified disease status. Verification bias leads to inflated estimates of sensitivity (true positives) and decreased estimates of specificity (true negatives) (13).

The presence of verification bias in WISE complicates the assessment of the relationship between symptoms and CAD, as symptom evaluation remains an important screening tool for angiography. There is some evidence in the WISE sample for verification bias. For example, 70% of WISE women have either typical or atypical angina, indicating that physicians are less likely to refer women for coronary angiograms with

nonanginal symptoms. Moreover, the nonanginal women have the same high rate of CAD risk factors (Table 1) and list the same reasons for referral to angiography as the anginal women, including symptoms (98% vs. 98%) abnormal stress test (51% vs. 52%) but less shortness of breath (51% vs. 63%).

The effect of verification bias would be to overestimate sensitivity, the prevalence of disease, and the prevalence typical angina as compared to the general (unverified plus observed) symptomatic population. At face value, the magnitude of this bias is difficult to test as we do not have access to the distribution of anginal symptoms in the symptomatic but unverified population. However, we do know that the sensitivity for typical angina in WISE is 43%. If this is an over-estimate then the "true" sensitivity in the complete population would be even lower. The presence of verification bias would therefore not contradict our assertion that a majority of women with CAD do not have typical angina.

Another issue is the low disease prevalence (26%) in our WISE sample which, because of verification bias, may be an overestimate of the true prevalence in the total symptomatic population without prior history of CAD. Since predictive accuracy is a function of disease prevalence in the overall population, it is expected to be quite low in our sample. Moreover, since both age and anginal type may have different distributions in the larger population, our age*angina stratification may not result in the "true" distribution of CAD across these categories. However, the fact remains that 74% of our WISE population who were referred for angiography did not have CAD.

e. Implications. Our results suggest that a diagnosis of typical angina plays an important part in the referral of patients for angiography, leading to possible verification (referral) bias, which however does not contradict our findings that typical angina has a low sensitivity for CAD in women. The absence of a reliable symptom yard stick for women is costly both in terms of morbidity and healthcare utilization. By the time women are diagnosed with significant CAD they typically have greater disease severity and disability than men (14-15). In fact, women are more likely to die from an episode of myocardial infarction than men (16-18). Current chest pain evaluation, as part of the typical clinical history work-up, has led to a situation where too few women with CAD are being diagnosed in a timely manner and a large number of women without CAD are receiving angiograms. The high rate of normal angiograms in women presents an interesting challenge to society and clinician alike. The cost of normal angiograms has been estimated to be over $134 million dollars annually. Moreover, about half the women with normal coronaries continue to have persistent symptoms and require costly medical evaluation and care (19).

This begs the question of possible reasons for the paradox of high rates of classic symptoms and low rates of CAD in women undergoing angiography. Aside from being a possible artifact of verification bias or the possibility that classic angina assessment is simply not a good screening tool, it has been suggested that symptoms in the absence of CAD may in fact be a sign of microvascular ischemia. WISE is currently evaluating the pathophysiological basis, traditional and novel test strategies, prognostic implications, and potential role in disease progression of this as yet poorly understood condition.

3. Current challenges and the most important issues for future research

a. For women with angina and normal coronaries, what is the clinical significance of their symptoms? The mechanisms for chest pain in the absence of CAD is not well understood. A number of possibilities have been offered by other investigations:

(i) Symptom of psychological distress. Women with normal coronary symptoms and persistent symptoms have a higher prevalence of depression, anxiety, panic disorder, and somatization. However, WISE results suggest that such psychological distress may be secondary to the presence of unexplained symptoms (20).

(ii) Heightened pain perception and somatic awareness in women. Recent data have demonstrated that women, compared to men, have decreased pain thresholds and are more likely to report symptoms to

physicians. Such findings may help explain sex-related differences in clinical presentation (21).

(iii) Microvascular ischemia. Even after ruling out gastrointestinal disorders and a variety of other possible physical and emotional causes, there remains a high percentage of women with severe and disabling symptoms that can persist for years (22). WISE has confirmed recent evidence that much of women's chest discomfort in the absence of CAD may be due to a higher prevalence among women of microvascular angina, due to functional and metabolic abnormalities of the coronary microcirculation during stress (23-24). It is believed that the mechanisms of chest pain may be similar for both CAD and microvascular ischemia (25).

b. Is there a "Female Angina" Pattern? Results from the WISE confirm that women with CAD experience a wide variety and quantity of symptoms. Moreover these differ by age. For women above age 55, neck pain and left chest pain were negatively associated with CAD while onset during upper body exertion was positively associated with CAD. Younger women with CAD experienced an array of significant symptoms, primarily focused on the arm , shoulders, and hands. They had non-specific triggers and sources of relief, and numbness was a positive predictor while weakness, fatigue, or faintness was a negative predictor. These symptoms predicted CAD better than the "typical angina" measure among both groups of women. These findings will need to be verified in other populations, but they highlight the importance of developing a better diagnostic symptom tool specifically tailored for women.

c. What is the role of endogenous reproductive hormones in the nature and presentation of CAD symptoms? Physiological differences between men and women may be modulated by the different reproductive hormones. In women, menopausal status is considered an independent predictor of CAD (26-27). Data suggests that premenopausal women have a low risk of CAD, while postmenopausal women have a risk similar to that of men. Improved understanding of the role of endogenous hormones in the development and presentation of CAD will improve risk stratification of women for CAD.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

a. Clinician attitudes. There may be a reluctance in the medical community to accept that there may be pathophisiological differences between male and female patients. Women reporting with "non-classic" symptoms may not be taken seriously and may not be evaluated for their complaints (28).

b. Clinician bias. Persistence of the Freudian "female hysteria" model. Studies have shown that communication style may affect a woman's assessed probability of CAD (29).

c. Lack of knowledge by women of their risk of coronary heart disease, and inability to recognize their symptoms as possible CAD. Underestimating their own risk of CAD, women are likely to ignore their symptoms and delay seeking medical care (30-32).

5. Translating new findings to improved diagnosis and treatment/saving lives.

a. Improve physician awareness: (a) of the importance of heart disease in women; (b) of differences in symptom presentation between men and women and between younger and older women. These differences must be taken into consideration for appropriate medical management.

b. Stress the importance of further evaluation after CAD has been ruled out, to evaluate for vasospastic and microvascular angina.

c. Goal: to develop a female angina evaluation tool. The characterization of signs and symptoms of myocardial ischemia specific to women may assist physicians make more appropriate referrals for angiography. The development of such a tool remains a major challenge.

6. References.

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Table 1. Baseline Characteristics of WISE Sample

Characteristic	% or Means (SD)
Age (years)	57 (11)
CAD	26%
Postmenopausal	73%
Non-White	17%
Body Mass Index	29.6 (6.5)
Current Smoking	18%
Ever Smoked	50%
Diabetes	19%
Hx. Dyslipidemia	47%
History of Hypertension	54%
Systolic Blood Pressure	136 (20)
Family History of CAD	67%
# CAD Risk Factors	1.8 (1.4)
0	18%
1	31%
2	24%
3+	27%

Table 2. Percent of WISE Women with Angina Classifications by CAD

Angina Classification	No CAD n=409	CAD n=148	p
Typical Angina (n=186)	30%	43%	0.003
Atypical Angina (n=202)	38%	31%	0.12
Non-Anginal (n=130)	23%	24%	0.92
Asymptomatic (n=39)	9%	2%	0.006

Table 3. Percent of WISE Women with Classic Angina Indicators by CAD, Stratified by Age

Variable	No CAD	CAD	p
1. Age ≥ 55 Years:	**n=201**	**n=111**	
Substernal	65%	75%	0.08
Effort / Stress	53%	66%	0.02
Rest / NTG	67%	80%	0.01
Typical Angina (all 3 above)	28%	47%	0.001
2. Age < 55 Years:	**n=208**	**n=37**	
Substernal	63%	62%	0.92
Effort / Stress	52%	59%	0.40
Rest / NTG	78%	78%	0.95
Typical Angina (all 3 above)	31%	32%	0.89